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### Mitigation of Investigator Bias in Adverse Event Reporting from an Industry-sponsored Spine Surgery Study: Utilization of an Independent Clinical Events Committee

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**Introduction:** Recent articles in the lay press and in peer-reviewed publications have raised concerns about the ability to report high quality, unbiased adverse event data from an industry-sponsored spine surgery study where investigators may have a perceived conflict of interest. To address this, many clinical trials utilize an independent clinical events committee (CEC) to review adverse events and re-adjudicate the severity and relatedness accordingly. No study to date has demonstrated or quantified the degree to which bias is present in adverse event reporting, nor the effect that a CEC has on mitigating this potential bias.

**Methods:** The coflex® IDE study is a prospective, randomized, multicenter trial comparing coflex® device (n=140 patients) to laminectomy and posterolateral fusion (n=72 patients) for the treatment of spinal stenosis with spondylolisthesis. Investigators classified the severity of each adverse event (mild, moderate, or severe), and the relationship to surgery and device (unrelated, unlikely, possibly, probably, or definitely). An independent CEC, composed of 3 independent, blinded spinal surgeons without affiliation to the study sponsor, reviewed and re-adjudicated all adverse events. All CEC adjudications were binding to the sponsor.

**Results:** The CEC reclassified the level of severity, relation to surgery, and/or relation to device of 394 of the 1,056 (37.3%) adverse events. A similar proportion of adverse events were reclassified in the coflex® and fusion groups (37.9% vs. 36.0%, p=0.56). Similar rates of reclassification were also observed between the coflex® and fusion groups with respect to level of severity (6.3% vs 3.3%, p=0.06), relation to surgery (28.7% vs 27.1%, p=0.59), and relation to device (25.8% vs 27.4%, p=0.59). Conditional on CEC revising the investigators' original rating, it was 5.3 (95% CI 2.6 to 10.7) times more likely for the CEC to upgrade the adverse event than to downgrade the adverse event. Similarly, it was 7.3 (95% CI 5.1 to 10.6) times more likely for the CEC to upgrade the relationship to surgery and 11.6 (95% CI 7.5 to 18.8) times more likely for the CEC to upgrade rather than downgrade the relationship to the device (Table).

**Table: CEC Revisions of Investigator Classification of Adverse Events with Revision Outcome (in relation to total adverse events)**

	coflex® (N=752)		p value <sup>1</sup>	Fusion Control (N=303)		p value <sup>1</sup>	Total (N=1,056)		OR <sup>2</sup> (95% CI)
	n	%		n	%		n	%	
Level of Severity	47			10			57		
<i>Upgraded</i>	38	80.9%	<0.0001	10	100%	0.002	48	84.2%	5.3 (2.6 to 10.7)
<i>Downgraded</i>	9	19.1%		0	0.0%		9	15.8%	
Relation to Surgery	216			82			298		
<i>Upgraded</i>	188	87.0%	<0.0001	74	90.2%	<0.0001	262	87.9%	7.3 (5.1 to 10.6)
<i>Downgraded</i>	28	13.0%		8	9.8%		36	12.1%	
Relation to Device	194			83			277		
<i>Upgraded</i>	180	92.8%	<0.0001	75	90.4%	<0.0001	255	92.1%	11.6 (7.5 to 18.8)
<i>Downgraded</i>	14	7.2%		8	9.6%		22	7.9%	

**Notes:**

<sup>1</sup> Two-sided z-test of null hypothesis that when CEC revise a status it is equally likely for the CEC to upgrade or downgrade the characteristic.

<sup>2</sup> Odds ratio and Clopper-Pearson (Exact) binomial 95% confidence limits.

[Table]

Further break-down of the adverse event reports of the coflex® trial demonstrated that the status of the investigator's financial interest in the company had little effect on the reclassification of adverse events. Similar rates of adverse events were reclassified in both investor and non-investor groups (37.2% and 37.4%, respectively).

**Conclusions:** Our results demonstrate substantial investigator bias in the reporting of adverse events. A total of 37% of adverse events were revised by the CEC, the vast majority of which were upgrades in the level of severity, or a designation of greater relatedness to surgery or device. An independent CEC can identify and mitigate potential inherent investigator bias and facilitate an accurate assessment of investigational device safety profile, and further, should be considered a requisite component of future clinical trials.